REMARKS

Amended

The cross-references paragraph has been updated to claim priority directly to USSN 08/615,369 which has now issued as US Patent No. 6,267,958 ("the '958 patent"). An executed substitute declaration is filed herewith which includes the updated priority information.

Turning now to the claim amendments, the typographical errors in claims 29 and 42 are corrected herein. Claim 51 has been added which reflects a combination of claim 37 and claim 29. To accelerate prosecution, the colon indication is removed from claim 37, and claim 39 now depends on new claim 51.

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

Section 112, first paragraph

Claims 26, 28-34 and 37-50 are rejected under 35 USC Section 112, first paragraph as allegedly lacking enablement in that the specification "does not provide clear direction as to how the formulation can be used for the treatment of cancer."

The Examiner states that it is well known in the art that anti-HER2 antibodies are used for the treatment of certain types of cancer, such as breast cancer, but contends that the "formulation for the anti-HER2 antibody as disclosed in the claims or specification may not function in the same manner as other efficacious anti-HER2 antibodies already in the prior art." The Examiner urges that the addition of other additives such as lyoprotectants and bulking agents, may render the product ineffective.

Applicants respectfully submit that the presently claimed invention is enabled by the instant specification. The specification describes formulations comprising an antibody which binds HER2 receptor (see entire disclosure, including Example 1 on pages 25-37 of the specification), and

provides guidance as to administration of such formulations to treat cancer (see, in particular, pages 23-24). Applicants submit that the person skilled in the art at the time of filing, would have been able to treat endometrial cancer, lung cancer, colon cancer, bladder cancer or ductal carcinoma *in situ* (DCIS) with the formulation, based on the teachings of the present application without undue experimentation.

A variety of different formulations are described. One preferred formulation of the anti-HER2 antibody was rhuMAb HER2 at 25mg/mL, 60mM trehalose, 5 mM histidine pH 6 and 0.01% polysorbate 20 (line bridging pages 36-37). Applicants rely on objective evidence in the form of the attached Product Information for rhuMAb HER2 (HERCEPTIN®) as confirming that the described formulations, including this preferred formulation, are efficacious, and that the additives do not render the product ineffective. As noted in the paragraph under the heading "Description" in the attached Product Information, the HERCEPTIN® formulation is that which is described in the line bridging pages 36-37 of the instant application. As demonstrated by the marketing approval of the formulated HERCEPTIN® product for treating cancer, such as breast cancer, Applicants submit that the efficacy of the presently claimed methods is convincingly demonstrated. Clearly the additives do not render the product ineffective.

Reconsideration and withdrawal of the enablement rejection is respectfully requested.

Section 103

Claims 26, 28-34, and 37-41 are rejected under 35 USC Section 103(a) as being unpatentable over Valone *et al. J. Hematother* 4(5):471-5 (1995), in view of Press *et al. Oncogene* 5(7):953-62 (1990), and Natali *et al. Int. J. Cancer* 45(3):457-61 (1990), and further in view of Burton *et al. Am. J. Vet. Res.* 42(2):308-10 (1981).

Valone *et al.* is said to teach patients suffering from advanced breast or ovarian cancer using a bispecific antibody to FcRI receptors and HER2.

Press *et al.* is said to teach the examination of HER2 expression in normal fetal and adult human tissues, and the potential to use HER2 antigen as a diagnostic and therapeutic agent by examining alterations in expression levels of this protein in human tumors.

Natali *et al.* is relied on as teaching the expression of HER2 in normal and transformed human tissues, the immunohistochemical examination of normal tissue and various tumors with monoclonal anti-HER2 antibodies, with positive staining results in breast, ovary and colon, and the use of HER2 as a tumor marker.

The Examiner acknowledges that Valone *et al.*, Press *et al.* and Natali *et al.* do not teach the use of a lyophilized formulation of an anti-HER2 antibody, and cites to Burton *et al.* as teaching the use of a lyophilized serum for immunization of neonatal foals.

The Examiner concludes that it would have been *prima facie* obvious to combine the teachings of the cited art to derive a treatment of cancers using an antibody directed against HER2 that was lyophilized, and one would have been motivated to combine the references because the use of an anti-HER2 antibody for the treatment of cancer was well known in the art as an efficacious treatment of ovarian and breast cancer types, and that one would expect that a reasonable amount of success would have been achieved if one combined the teachings to treat cancer using an anti-HER2 antibody for endometrial, lung, colon, bladder, and ductal carcinoma *in situ*. The Examiner urges that it would have been obvious to combine the teaching set forth above with those of Burton *et al.* to make an antibody that was in a lyophilized form to administer to cancer patients.

In order to advance prosecution, claim 37 is amended herein to refer to treatment of endometrial, lung, or bladder cancer. Applicants submit that claim 37 herein was not obvious over the cited art. The relied-upon art refers only to breast, ovarian and colon cancer. There is absolutely no suggestion in the relied upon art to treat endometrial, lung, or bladder cancer in a human comprising administering a therapeutically

effective amount of a formulation comprising an antibody which binds HER2 receptor to the human. While the Examiner cites to Press *et al.*, Applicants note that this reference is concerned with *normal* tissues, rather than cancer tissue; there is certainly no suggestion in Press *et al.* to treat endometrial, lung, or bladder cancer using a formulation comprising an antibody which binds HER2 receptor.

As to claim 42 and its dependent claims, Applicants note that these claims are not rejected over the cited art. Since, as demonstrated above, these claims are enabled, Applicants submit that they are therefore allowable.

Finally, with regard to claim 51 herein, this claim references the preferred formulation, which has previously been found to be patentable over the art (see claim 26 of the '958 patent).

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested in view of the above.

A Supplemental IDS is filed herewith. Applicants respectfully request consideration of the art in relation to the present application. In addition a Statement of Related Cases accompanies the present amendment. Applicants respectfully invite the Examiner to consider the related cases with respect to the present application.

Applicants believe that the present application is now in condition for allowance and look forward to early notification to that effect. If, however, there are outstanding issues to be resolved, the Examiner is invited to call the undersigned to discuss those and, therefore, advance allowance of the present application.

Respectfully submitted,

GENENTECH, INC.

Date: June 17, 2002

By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please replace the paragraph starting on page 1, line 7 with the following:

--This is a divisional of [application serial number 09/273,230 filed March 18, 1999, which is a divisional of] application serial number 08/615,369 filed March 14, 1996, now U.S. Patent 6,267,958 issued July 31, 2001, which claims priority under §119(e)(1) to provisional application number 60/029,182 filed July 27, 1995, [all] both of which are incorporated herein by reference.--

IN THE CLAIMS:

Please amend the claims as follows.

29. (Amended) The method of claim 37 wherein the fomulation comprises the antibody in an amount from about 5-40 mg/mL, sucrose or trehalose in an amount from about 10-100 mM, a buffer and a surfactant.

37. (Amended) A method for treating a cancer selected from the group consisting of endometrial, lung, [colon] and bladder cancer in a human comprising administering a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor to the human.

39. (Amended) The method of claim [37] 51 wherein the cancer is lung cancer.

42. (Amended) A method for treating ductal carcinoma *in situ* in a human comprising administering a [therapeutially] therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor to the human.

Please add the following claim:

-- 51. (New) A method for treating a cancer selected from the group consisting of endometrial, lung, colon, and bladder cancer in a human comprising administering a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor to the human, wherein the formulation comprises the antibody in an amount from about 5-40mg/mL, sucrose or trehalose in an amount from about 10-100mM, a buffer and a surfactant.--